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α1 and α2-adrenoceptors in the medial amygdaloid nucleus modulate differently the cardiovascular responses to restraint stress in rats

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ABSTRACT

Medial amygdaloid nucleus (MeA) neurotransmission has an inhibitory influence on cardiovascular responses in rats submitted to restraint, which are characterized by both elevated blood pressure (BP) and intense heart rate (HR) increase. In the present study, we investigated the involvement of MeA adrenoceptors in the modulation of cardiovascular responses that are observed during an acute restraint. Male Wistar rats received bilateral microinjections of the selective α1-adrenoceptor antagonist WB4101 (10, 15, and 20 nmol/100 nL) or the selective α2-adrenoceptor antagonist RX821002 (10, 15, and 20 nmol/nL) into the MeA, before the exposure to acute restraint. The injection of WB4101 reduced the restraint-evoked tachycardia. In contrast, the injection of RX821002 increased the tachycardia. Both drugs had no influence on BP increases observed during the acute restraint. Our findings indicate that α1 and α2-adrenoceptors in the MeA play different roles in the modulation of the HR increase evoked by restraint stress in rats. Results suggest that α1-adrenoceptors and α2-adrenoceptors mediate the MeA-related facilitatory and inhibitory influences on restraint-related HR responses, respectively.

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1. Introduction

Stress elicits both autonomic and behavioral responses, which involve an activation of the hypothalamo-pituitary–adrenal axis as well as the sympathetic nervous system [1]. Such responses are modulated by several limbic structures in the central nervous system [2–7]. Among these structures, the amygdaloid complex is known to modulate stress-related behavior and is connected with hypothalamic and brainstem areas that are involved with cardiovascular regulation [8–10]. In particular, the medial amygdaloid nucleus (MeA) of the amygdaloid complex is involved in the modulation of stress related responses and in cardiovascular control [1,11]. Electrical stimulation of the MeA was reported to evoke increased blood pressure and heart rate [12].

Stress is known to evoke cardiovascular changes that are characterized by moderate hypertension and intense tachycardia [4,7,13–20]. Pressor responses evoked by foot-shock in spontaneously hypertensive rats increased blood pressure and heart rate with contextual fear conditioning [6,21], while with exposure of borderline hypertensive rats to acute noise stress [22] they were reduced after electrolytic lesion of the amygdala, thus suggesting an involvement of the amygdala in the modulation of cardiovascular responses caused by stress. Moreover, increased c-fos expression in the MeA was observed after exposure to a number of stressors, such as a novel environment, swimming, social interaction and acute restraint stress [23,24].

MeA inhibition with muscimol was reported to attenuate the pressor response evoked during acute restraint [19]. Also, previous work from our laboratory showed that bilateral microinjection of the unspecific neurotransmitter blocker Cobalt chloride (CoCl2) into the MeA caused enhanced restraint-related tachycardiac response [4]. These data suggest the involvement of this area in cardiovascular modulation during stress.

The MeA receives substantial noradrenergic innervations originating in the A6 neurons in the locus coeruleus (LC) and other groups of noradrenergic neurons located in the lateral tegmental area [25,26]. Furthermore, studies of expression of mRNA and binding detected the presence of noradrenergic receptor subtypes α and β in the MeA [27,28], suggesting the existence of the noradrenergic system in this area.

Noradrenaline (NA) is a neurotransmitter with an important role in central cardiovascular regulation and is an important mediator in several structures of the central nervous system. Cardiovascular responses were observed after microinjection of NA into brain

Abbreviations: aCSF, artificial cerebrospinal fluid; ANOVA, analysis of variance; BP, blood pressure; HR, heart rate; MAP, mean arterial pressure; MeA, medial amygdaloid nucleus; PAP, pulsatile arterial pressure; RS, restraint stress.

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regions involved in the modulation of the cardiovascular system, such as the nucleus of the solitary tract (NTS); [29], the medial prefrontal cortex (CPFM); [30], the periaqueductal gray area (PAG); [31], the lateral septal area (ASL); [32], the bed nucleus of the stria terminal (BST); [33], the supraoptic nucleus (SON); [34] and the MeA [35].

Studies using microdialysis have shown increased levels of NA in several forebrain regions of the limbic system, mainly in the MeA of animals subjected to stress situations [1,36–40]. Although the noradrenergic system activation occurs in the MeA during stress, the role of this activation in the mediation of stress-induced cardiovascular responses has not yet been evaluated.

Several studies in the literature support the idea that acute restraint is an unavoidable aversive stimulus eliciting sustained BP and HR increase [41–46]. In this way, in the present study, we tested the hypothesis that noradrenergic neurotransmission within the MeA mediates the cardiovascular responses evoked by restraint stress. For that purpose, we pretreated the MeA with adrenoceptor antagonists and submitted the rats to acute restraint, after which we observed the cardiovascular responses evoked by this stressor.

2. Materials and methods

2.1. Subjects

Experimental procedures were carried out following protocols approved by the Ethical Review Committee of the School of Medicine of Ribeirão Preto (no. 057/2009). Male Wistar rats weighing 250–280 g were used in the present experiment. Animals were housed individually in plastic cages in a temperature-controlled room (25 °C) at the Animal Care Unit of the Department of Pharmacology, School of Medicine of Ribeirão Preto. Animals were kept under a 12:12 h light–dark cycle (lights on at 06:00). Animals had free access to water and standard laboratory food, except during the experimental period. Rats were transported to the experiment room and remained in their own cages until the experimental restraint procedure. Experiments were performed during the morning period to minimize possible circadian rhythm interferences.

2.2. Surgical preparation

Animals were anesthetized with tribromoethanol (250 mg/kg i.p.) and their heads were fixed to a stereotaxic apparatus (Stoelting, USA). The skull was surgically exposed and trepanned with a dental drill at a point located 3.4 mm from midline and 6.2 mm anterior to the interaural line, according to the rat brain atlas of Paxinos and Watson [47]. Bilateral stainless steel guide cannulae (26G, 15 mm-long) were lowered 8.0 mm from the skull. Guide cannulae were positioned 1 mm above the intended injection sites and fixed to the skull by a metal screw and dental cement. Animals were allowed to recover for 48 h before a polyethylene catheter was implanted into the femoral artery under anesthesia, for chronic recording of arterial BP and HR. The catheter was exposed on the dorsum of the animals and attached to the skin, allowing arterial pressure recording of unanesthetized rats 24 h after surgery.

2.3. Drug microinjection into the MeA

Injections were performed in a volume of 100 nL. For microinjections, we used a 1 μL syringe (KH7001, Hamilton, USA) connected to a 33G injection needle (Small Parts Inc, FL, USA) by PE-10 polyethylene tubing. The injection needle was 1.0 mm longer than the guide cannula.

2.4. Measurement of cardiovascular responses

Pulsatile arterial pressure (PAP) was recorded using an amplifier (model 7754A, Hewlett Packard, USA) coupled to a computerized acquisition system (MP100, Biopac, USA). Mean arterial pressure (MAP) and HR were derived from PAP data using the AcqKnowledge III Software (Biopac, USA). The MAP was calculated according to the equation: diastolic pressure + (systolic–diastolic)/3. The HR (beats/min; bpm) was calculated from PAP peak intervals that were integrated each 6 s.

2.5. Drugs utilized in the experimental procedures

The following drugs were used: Vehicle artificial cerebrospinal fluid (ACSF) had the following composition: 100 mM NaCl; 2 mM Na 3 PO 4; 2.5 mM KCl; 1 mM MgCl 2; 27 mM NaHCO 3; 2.5 mM CaCl 2 and pH = 7.4), RX821002 (α2-adrenoceptor antagonist), WB4101 (α1-adrenoceptor antagonist) urethane (Sigma, USA), tribromoethanol (Aldrich, USA), streptomycins and penicillins (Pentabiotico, Fort Dodge, Brazil), flunixine meglumine (Banamine, Schering Plough, Brazil).

2.6. Experimental procedure: acute restraint

Animals were transported to the experimental room in their home cages. They were allowed a 1 h period to adapt to the conditions of the experimental room, such as sound and illumination, before starting blood pressure and heart rate recording. The experimental room was acoustically isolated and had a constant background noise generated by an air exhauster. At least another 20 min period was allowed for baseline recording before experiments were initiated. After recording baseline values, bilateral microinjections of drugs or vehicle were made into the MeA, each animal receiving only one microinjection per brain side. Care was taken to start injection whenever a stable blood pressure and especially a stable heart rate recording were observed. The injection needle was slowly introduced through the guide cannula without touching or restraining the animals. Ten min later, the animals were submitted to restraint, which was initiated by putting animals into a small plastic cylindrical restraining tube (diameter = 6.5 cm and length = 15 cm). Restraint lasted for 60 min and immediately after, the animals were returned to their cages. Each animal was submitted to one session of restraint in order to prevent habituation.

Animals were divided into seven experimental groups: (1) aCSF group, vehicle microinjected into the MeA, (2) WB4101 dose 10 nmol group, (3) WB4101 dose 15 nmol group, (4) WB4101 dose 20 nmol group, (5) RX821002 dose 10 nmol group, (6) RX821002 dose 15 nmol group and (7) RX821002 dose 20 nmol group. The vehicle and all drugs were microinjected bilaterally into the MeA.

2.7. Histological determination of the microinjection sites

At the end of the experiments, animals were anesthetized with urethane (1.25 g/kg i.p.) and 100 nL of 1% Evan's blue was injected into the brain as a marker at the injection site. Animals were submitted to intracardiac perfusion with 0.9% NaCl followed by 10% formalin. Brains were removed, and post-fixed for 48 h at 4 °C and serial 40 μm-thick sections were cut with a cryostat (CM1900, Leica, Germany). Sections were stained with 1% violet cresyl for optical microscopy analysis. The actual placement of the microinjection needles was determined by analyzing serial sections, according to the rat brain atlas of Paxinos and Watson [47].

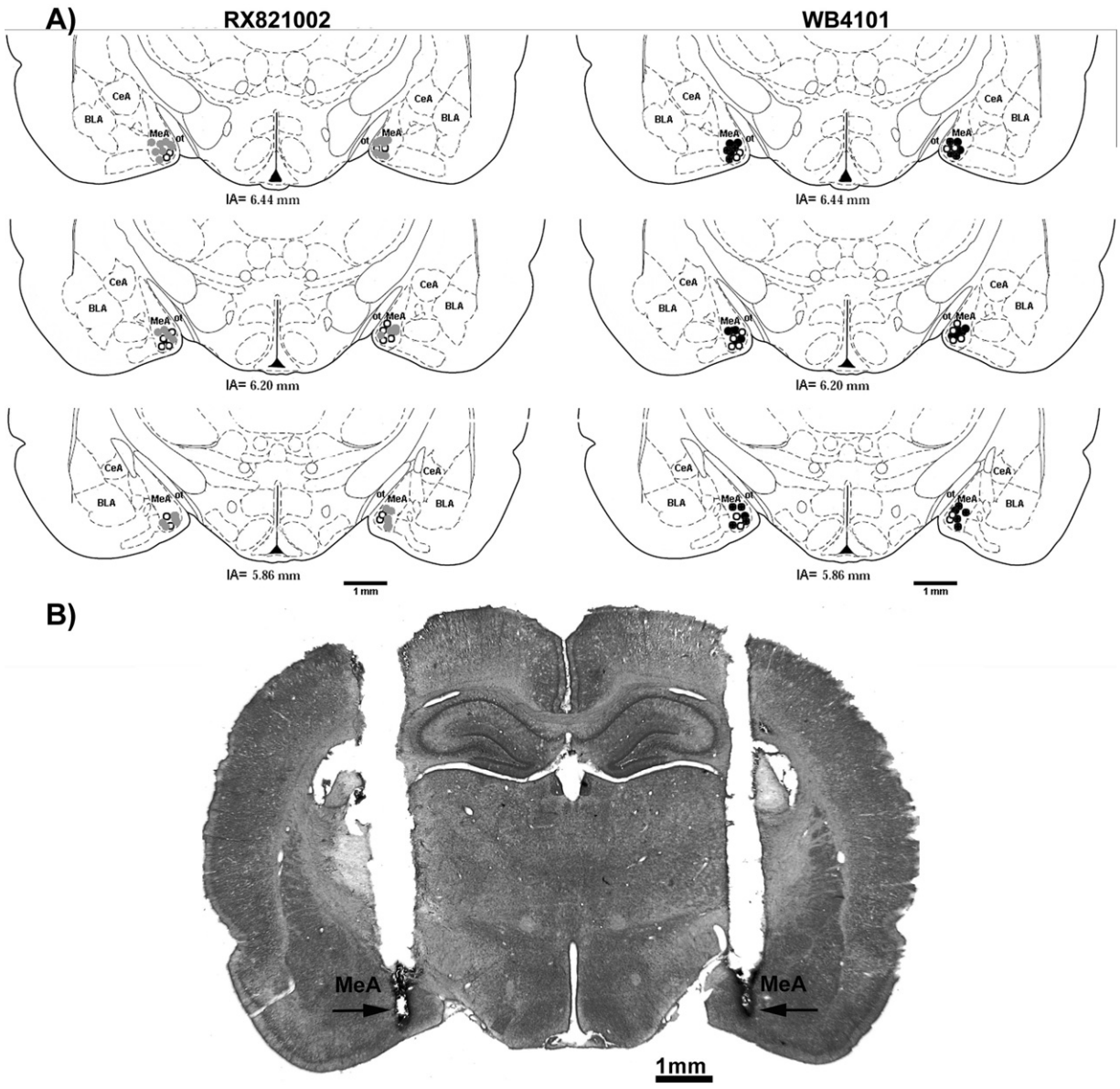

Fig. 1. (A) Diagrammatic representation modified from the rat brain atlas of Paxinos and Watson [47] indicating microinjection sites in the brain of rats used in the present experiment. Dots in the figure indicate microinjection sites of RX821002 (gray dots, left side), WB4101 (black dots, right side) and vehicle (white dots). (B) Photomicrograph of a coronal section of a representative rat brain showing the sites of bilateral microinjections in the MeA, which are indicated by arrows. IA – interaural, CeA – central nucleus of the amygdala; BLA – basolateral nucleus of the amygdala; OT – optic tract.

2.8. Statistical analysis

Statistical analysis was performed using Prism software (GraphPad, USA). The paired Student's *t*-test was used to compare basal MAP and HR values before and after aCSF or drug treatment. To determine and compared ΔMAP and ΔHR changes, we used one-way ANOVA followed by Dunnett's test, to verify alterations between aCSF and drug treatments.

Although blood pressure was recorded throughout the experimental procedure, curves for statistical analysis or illustrative figures were generated with points obtained from different data sampling. Figs. 3 and 4 were generated from samplings of 0.64/min for more accurate representation. To verify possible correlations between drug doses and ΔMAP or ΔHR values, we used linear regression curves that were generated from selected points recorded during the 60 min restraint stress period. The significance was set at $p < 0.05$. Data are presented as mean ± SEM.

3. Results

3.1. Determination of microinjection sites

A diagrammatic representation showing microinjection sites in the MeA of the animals used in the study is presented in Fig. 1A. A photomicrograph of a coronal brain section depicting bilateral microinjection sites in the MeA of one representative animal is presented in Fig. 1B.

3.2. Effect of MeA pretreatment with the selective α_1-adrenoceptor antagonist WB4101 on restraint-related cardiovascular changes

Bilateral microinjection of WB4101 (10, 15 and 20 nmol/100 nL) did not affect baseline BP and HR values when compared with aCSF-treated animals (Tables 1 and 2). The pretreatment with WB4101 significantly reduced the restraint-evoked ΔHR increase

Table 1
Basal values of the mean arterial pressure (MAP), before and after the microinjection of different doses with WB4101 (selective α_1-adrenoceptor antagonist) into the MeA of the rats.

WB4101 (nmol/100 nL)	Before (MAP) ± SEM (mmHg)	After (MAP) ± SEM (mmHg)	*t* =	*n* = (sample)
0	96 ± 4	94 ± 3	0.2683	8
10	101 ± 4	100 ± 6	0.01702	5
15	86 ± 1	88 ± 1	0.7759	5
20	91 ± 1	87 ± 2	1.262	7

Table 2
Basal values of the heart rate (HR), before and after the microinjection of different doses with WB4101 (selective α_1-adrenoceptor antagonist) into the MeA of the rats.

WB4101 (nmol/100 nL)	Before (HR) ± SEM (bpm)	After (HR) ± SEM (bpm)	*t* =	*n* = (sample)
0	366 ± 8	358 ± 5	0.8270	8
10	330 ± 16	334 ± 8	0.2197	5
15	361 ± 13	370 ± 10	0.5522	5
20	370 ± 7	375 ± 5	0.5746	7

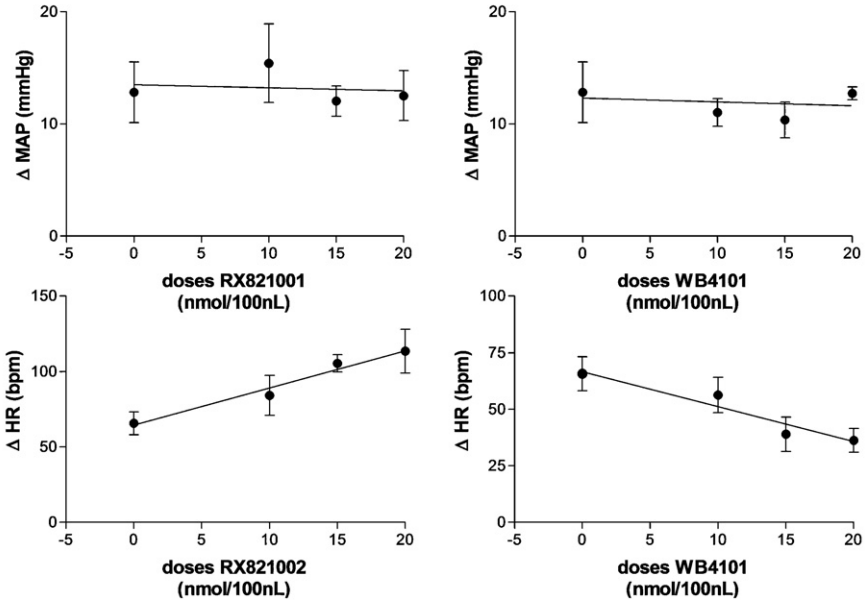

Fig. 2. Mean arterial pressure (ΔMAP) and heart rate (ΔHR) changes in response to the injection of increasing doses of RX821002 (left side) and WB4101 (right side) 10, 15 and 20 nmol/100 nL in rats. Dose zero: vehicle (aCSF-treated,). Dose–effect curves were generated by linear regression analysis. Data shown represent the means ± SEM of the variation of MAP and HR during the 60 min of acute restraint.

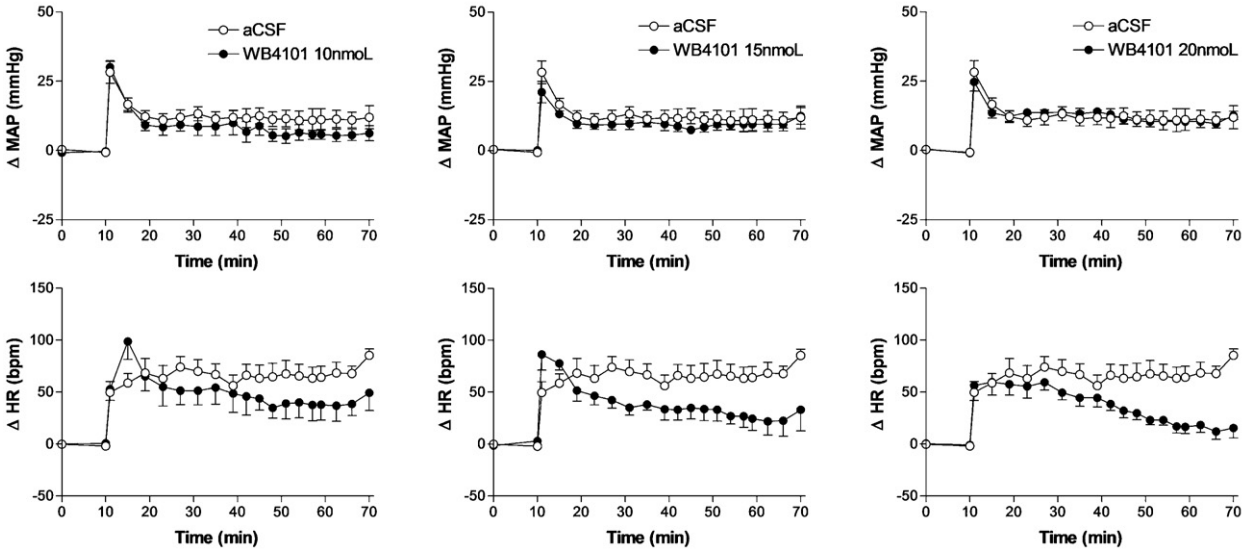

Fig. 3. Effects of different doses of (WB4101 – 10, 15 and 20 nmol, *n* = 5, 5, 7 per group, respectively) or vehicle (aCSF-treated, *n* = 8) on changes in mean arterial pressure (ΔMAP) and heart rate (ΔHR) of animals submitted to 60 min of restraint stress. The minute 10 indicates the beginning of the restraint period. Data shown represent the means ± SEM. $P < 0.05$, compared with vehicle group; ANOVA followed by Dunnett's post hoc test.

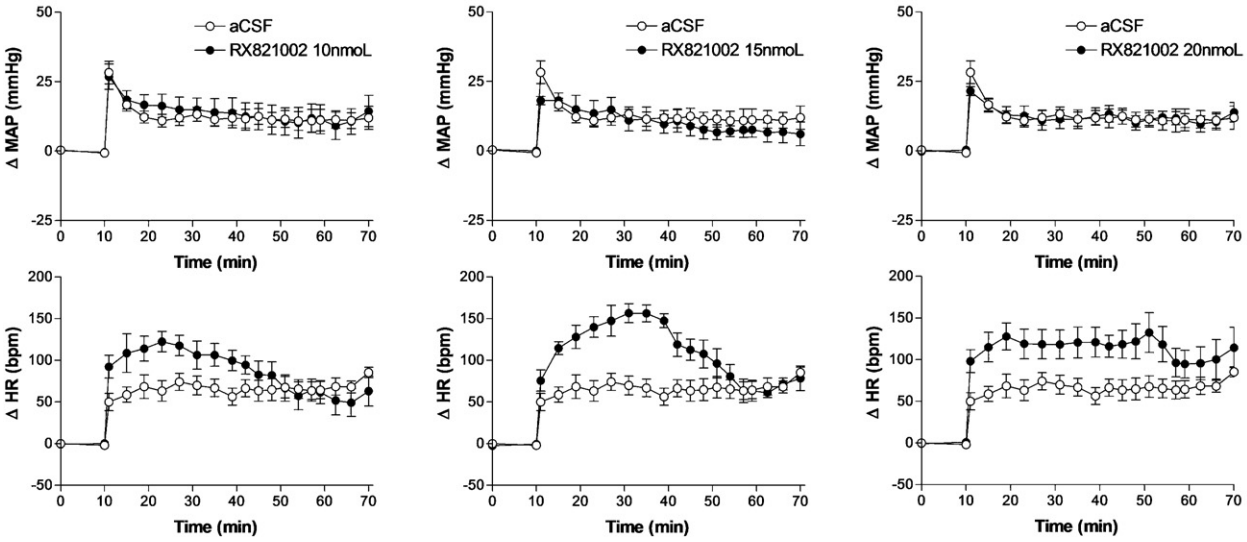

Fig. 4. Effects of different doses of (RX821002 – 10, 15 and 20 nmol, $n = 6$, 5, 6 per group, respectively) or vehicle (aCSF-treated, $n = 8$) on changes in mean arterial pressure (ΔMAP) and heart rate (ΔHR) of animals submitted to 60 min of restraint stress. The minute 10 indicates the beginning of the restraint period. Data shown represent the means ± SEM. $P < 0.05$, compared with vehicle group; ANOVA followed by Dunnett's post hoc test.

at doses of 15 and 20 nmol (ΔHR, $F_{3,21} = 4.267$, $P < 0.05$) without a significant effect on the ΔBP response, when compared with aCSF-treated animals (ΔMAP $F_{3,21} = 0.3792$, $P > 0.05$). The dose of 10 nmol did not evoke a difference in restraint-related ΔMAP or ΔHR increases when compared with aCSF-treated animals ($P > 0.05$). A dose-dependent relation was evidenced by linear regression analysis with a significant correlation between doses and the attenuation in the ΔHR increase during restraint ($r^2 = 0.35$, df = 23, $P < 0.05$) without a significant effect on the ΔBP response ($r^2 = 0.0003551$, df = 23, $P > 0.05$) (Fig. 2). Recordings showing the cardiovascular response of a rat pretreated with aCSF or WB4101 (15 nmol/100 nL) in the MeA and submitted to acute restraint are presented in Figs. 3–5.

3.3. Effect of MeA pretreatment with the selective α_2-adrenoceptor antagonist RX821002 on restraint-related cardiovascular changes

Bilateral microinjection of RX821002 (10, 15 and 20 nmol/100 nL) did not affect baseline BP and HR values when compared with aCSF-treated animals (Tables 3 and 4). Pretreatment with RX821002 significantly enhanced the restraint-evoked ΔHR increase at doses of 15 and 20 nmol (ΔHR, $F_{3,21} = 4.287$, $P < 0.05$) without a significant effect on the BP response, when compared with aCSF-treated animals (ΔMAP $F_{3,21} = 0.2910$, $P > 0.05$). The dose of 10 nmol did not evoke changes in restraint-related ΔMAP or ΔHR increases when compared with aCSF-treated

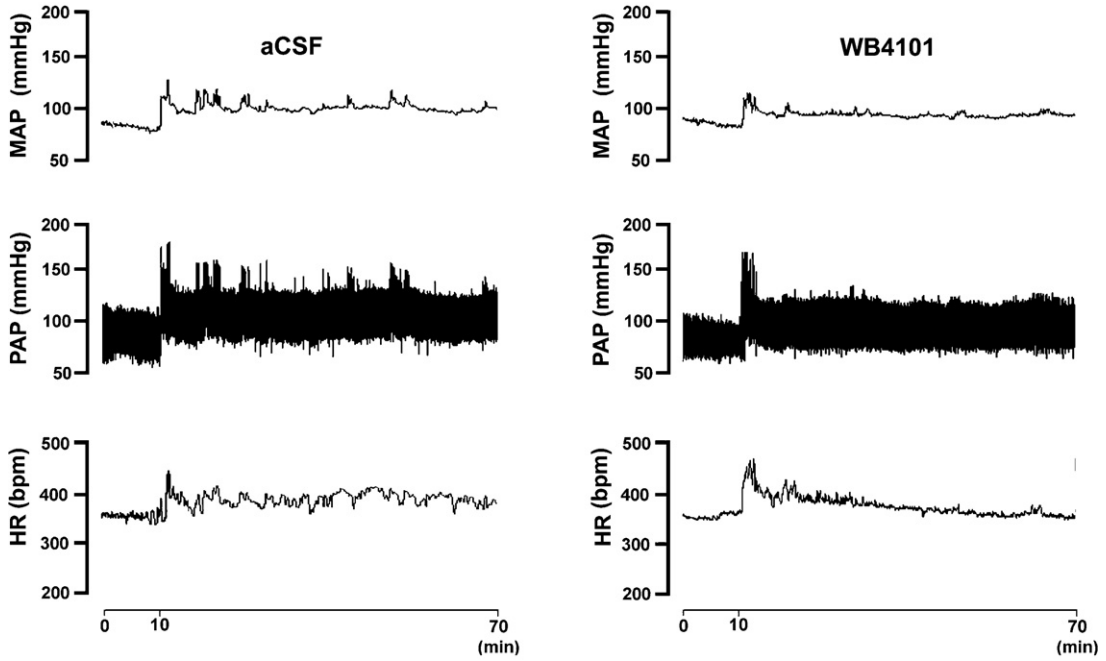

Fig. 5. Recordings of mean arterial pressure (MAP), pulsatile arterial pressure (PAP) and heart rate (HR) showing the cardiovascular changes observed before and during a restraint period of 60 min in a control rat and in a rat whose MeA was treated with WB4101 – 15 nmol/100 nL before restraint. The onset of restraint was at $t = 10$ min.

Table 3
Basal values of the mean arterial pressure (MAP), before and after the microinjection of different doses with RX821002 (selective α_2-adrenoceptor antagonist) into the MeA of the rats.

RX821002 (nmol/100 nL)	Before (MAP) ± SEM (mmHg)	After (MAP) ± SEM (mmHg)	t =	n = (sample)
0	96 ± 4	94 ± 3	0.2683	8
10	104 ± 3	101 ± 4	0.4893	6
15	93 ± 3	92 ± 5	0.1785	5
20	87 ± 4	90 ± 5	0.5337	6

Table 4
Basal values of the heart rate (HR), before and after the microinjection of different doses with RX821002 (selective α_2-adrenoceptor antagonist) into the MeA of the rats.

RX821002 (nmol/100 nL)	Before (HR) ± SEM (bpm)	After (HR) ± SEM (bpm)	t =	n = (sample)
0	366 ± 8	358 ± 5	0.8270	8
10	356 ± 7	355 ± 8	0.1257	6
15	351 ± 8	363 ± 11	0.8194	5
20	355 ± 9	367 ± 7	0.9843	6

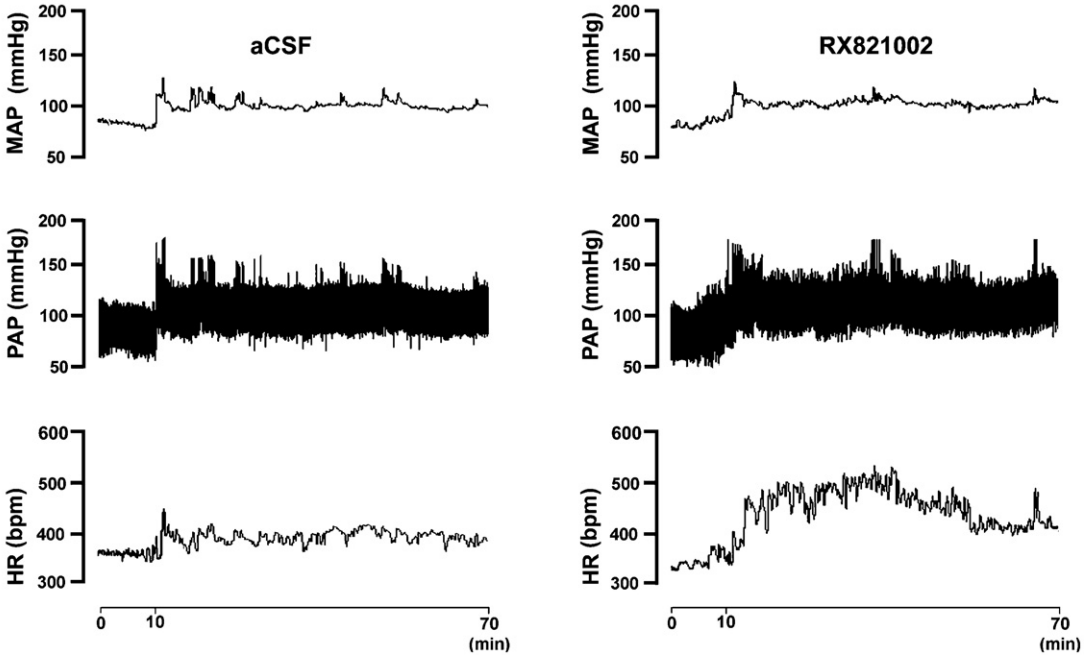

Fig. 6. Recordings of mean arterial pressure (MAP), pulsatile arterial pressure (PAP) and heart rate (HR) showing the cardiovascular changes observed before and during a restraint period of 60 min in a control rat and in a rat whose MeA was treated with RX821002 – 15 nmol/100 nL before restraint. The onset of restraint was at t = 10 min.

animals ($P > 0.05$). A dose dependency was evidenced by linear regression analysis that showed a significant correlation between doses and enhancement in the ΔHR increase ($r^2 = 0.3703$, df = 23, $P < 0.05$) without a significant effect on the ΔBP response ($r^2 = 0.001064$, df = 23, $P > 0.05$) (Fig. 2). Recordings showing the cardiovascular response of a rat pretreated with aCSF or RX821002 (15 nmol/100 nL) in the MeA and submitted to acute restraint are presented in Fig. 6.

4. Discussion

To study the possible involvement of noradrenergic neurotransmission in the MeA in the modulation of restraint-evoked cardiovascular responses, we pretreated this area with different doses of selective α-adrenoceptor antagonists. Bilateral microinjection of WB4101, a selective α_1-adrenoceptor antagonist, into the MeA caused a significant reduction in tachycardia evoked by acute restraint. The effect of WB4101 on the restraint-evoked HR response was dose-dependent. Pretreatment with WB4101 had no significant effect on the restraint-evoked pressor response. In contrast, pretreatment with RX821002, a selective α_2-adrenoceptor antagonist, significantly increased the restraint-evoked tachycardiac response, in a dose-related manner. Pretreatment with RX821002 did not affect the restraint-evoked pressor response.

The drugs used in our study did not affect baseline BP or HR, thus indicating that the MeA does not contribute to cardiovascular control at rest. These results corroborate previous data from the literature indicating no changes in cardiovascular responses after microinjection of these antagonists into the MeA or other brain structures [4,19].

Restraint is an inescapable stressful stimulus that causes cardiovascular changes that are characterized by both BP and HR increases [7,19,41,48–50]. The idea of a MeA involvement in the mediation of stress-evoked responses is reinforced by data from the literature showing that its electrical stimulation activates the hypothalamic–pituitary–adrenal HPA axis in anesthetized rats [51]. Moreover, the MeA is connected with hypothalamic and brainstem areas that are involved in cardiovascular regulation [8–10].

Structures such as the lateral septal area [20,52], lateral hypothalamus [53,54], medial prefrontal cortex [7], bed nucleus of stria terminalis [3], MeA and central amygdala (CeA) [4,19,50] and the paraventricular nucleus of the hypothalamus (PVN) [56,57]

were proposed to be part of the circuitry that modulates restraint-evoked cardiovascular responses. Data from the literature also indicate a larger activation of the MeA, among other amygaloid nuclei, during stressful situations, as is indicated by the large expression of c-fos protein in this area after exposure to aversive situations [19,48,58–64].

Inhibition of the MeA with muscimol attenuated the restraint-evoked pressor response [19]. In addition, in a previous study from our group, it was shown that bilateral microinjection of the non-selective synaptic blocker $CoCl_2$ into the MeA increased the HR response to acute restraint, without a significant effect on the BP response [4]). Together, these data suggest that the MeA is involved in the modulation of cardiovascular responses evoked by acute restraint.

Besides activating the HPA axis and the sympathetic nervous system, exposure to stress also induces a noradrenaline (NA) release, which facilitates synaptic transmission in many of the brain regions involved in modulation of stress-related behavioral and physiological responses [65–67]. The NA may affect HPA reactivity not only by acting directly on the PVN [68–70], but also through actions in extrahypothalamic regions that exert a modulatory input on the HPA axis. For example, it has been shown that noradrenergic neurotransmission is activated in the MeA under acute immobilization stress, and that the NA released in MeA during stress facilitates the activation of the HPA axis [1]. The idea that the MeA participates in the extra hypothalamic circuitry facilitating the stress-induced HPA activation is consistent with previous reports showing that a direct stimulation of MeA increased corticosterone levels [51,71].

Studies on the expression of mRNA and receptor binding evidenced the presence of noradrenergic receptors in the MeA [27,28], thus suggesting the existence of a noradrenergic system in this area. The selective blockade of α_1-adrenoceptors by the microinjection of WB4101 (10, 15 and 20 nmol) into the MeA reduced, in a dose-dependent manner, the restraint-evoked HR response, without affecting the BP response. This result suggests that local α1-adrenoceptors play a facilitatory role on the restraint-evoked tachycardiac response in the rat. These data are different from those resulting from experiments performed with the administration of $CoCl_2$ into the MeA, in which there was an increased tachycardiac restraint-evoked response [4]. However, it is important to point out that $CoCl_2$ inhibits all synaptic neurotransmissions in the area. Selective antagonists such as WB4101 and RX821002 have been previously used to identify the subtype of α-adrenoceptor that is involved in the mediation of restraint-evoked pressor and tachycardiac responses when microinjected into the BST [3]. The present results indicate that local α_1-adrenoceptors in the MeA play an inhibitory role in the HR increase evoked by restraint stress.

The selective blockade of α_2-adrenoceptors by the microinjection of RX821002 (10, 15 and 20 nmol) into the MeA caused dose-dependent increases in the restraint-evoked tachycardiac response, similarly to that observed after the pharmacological ablation of the area with $CoCl_2$.

α2-Adrenoceptors are located both pre- and post-synaptically in the brain and are found in high density in the MeA [72,73]. The activation of α2-adrenoceptors results in the inhibition of neuronal firing and a decrease in NA release. Also, it is well known that selective α_2-adrenoceptor antagonists such as the RX821002, can either facilitate or potentiate the noradrenaline release in rats under basal conditions or during exposure to stress [74–80]. This can lead to increased levels of noradrenaline in rat brain areas such as the MeA [81–84]. Our results suggest that α_2-adrenoceptors in the MeA play an inhibitory influence on restraint-evoked tachycardiac responses in the rat.

α_2-Adrenergic binding sites have been detected in the MeA [72,73]. Moreover, previous data indicate that the cardiovascular response evoked by NA microinjection into the MeA involves local α_2-adrenoceptors [35], thus suggesting that in the MeA these receptors are involved with cardiovascular modulation.

The present results show that α1- and α_2-adrenoceptors in the MeA play different roles in the modulation of the cardiac response to acute restraint. Cardiac autonomic control is a result of a balance between parasympathetic and sympathetic activities [85]. Parasympathetic stimulation depresses HR and cardiac contractile force, whereas sympathetic activation increases it. However, simultaneous activation of both autonomic systems is associated with chemoreceptor, startle, noxious and defensive responses [86]. Stress-related cardiac and pressor responses are sympathetically mediated, because both are abolished after ganglion blockade and are respectively blocked by pretreatment with either β or α-adrenergic antagonists [87,88]. Moreover, previous results from the literature indicated that treatment with a parasympathetic blocker increased the tachycardiac response evoked by a psychological stress [3,7,89,90], thus suggesting a simultaneous activation of the cardiac parasympathetic and the sympathetic systems during psychological stress. An emotional–autonomic pathway has been localized in the extended amygdaloid complex of the rat. Microinjection of pseudorabies virus into the adrenal gland, stellate ganglion which regulates the heart, or celiac ganglion which innervates the gastrointestinal tract caused extensive transneuronal labeling in limbic system areas such as the extended amygdaloid complex, lateral septum, and infralimbic, insular, and ventromedial temporal cortical regions [91], suggesting that these areas are linked by multisynaptic connections to the sympathetic outflows.

Tachycardia evoked by restraint stress in rats is well documented [41,48,92]. There is evidence suggesting that the amygdaloid complex may be a part of the brain circuitry involved in this elevated cardiac sympathetic drive. Both electrical and chemical stimulation of the amygdala evoked heart rate increases [11,93–95], thus suggesting the involvement of this area in the modulation of cardiac responses.

5. Conclusion

In summary, we propose that in the rat, α_1-adrenoceptors in the MeA play a facilitatory role in the cardiac component of the restraint-evoked cardiovascular response whereas α_2-adrenoceptors have an inhibitory role in the modulation of the cardiac component of the response.

Conflicts of interest

None.

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